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2. Patent application number *(The Patent Office will fill in this part)* — 0309343.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

JAGOTEC AG
Eptingerstrasse 51
CH-4132 Muttenz
Switzerland

Patents ADP number *(if you know it)* — 8164840001

If the applicant is a corporate body, give the country/state of its incorporation — CH

4. Title of the invention

IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Kilburn & Strode
20 Red Lion Street
London
WC1R 4PJ

Patents ADP number *(if you know it)* — 125001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

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See note (d))

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11. I/We request the grant of a patent on the basis of this application.

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Kilburn & Strode

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr Nick C Bassil
Tel: 020 7539 4200

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IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS

The present invention is related to a medicament in the form of a tablet having a core containing an active agent and a compression coating surrounding the core.

Medicaments in the form of tablets and containing a core comprising active agent and a coating surrounding the core are well known in the art. Coatings are employed around active-containing cores for a variety of reasons. For example, they may effectively protect the active substance from aggressive physiological media prior to the delivery of the medicament to the preferred site of absorption, or they may be employed as a means of modulating the release of the active agent from the core. Coatings may also be employed for aesthetic purposes such as to include a flavourant as a means of masking a bitter-tasting active agent or excipients, or they may be used to impart colour or combinations of colour in order to act as a visual cue to a patient as to the nature of the medicament that is being taken, or as a means of branding.

Compression coating is one means of providing a medicament with a functional and/or aesthetic coating. Such coatings may be applied using all manner of industrial press-coating equipment well known in the art. Medicaments may be formed by adding a part of the coating material as a granulate into a die, and tamping the powder to form a base. Thereafter, an active agent-containing core is added to the die and sits on the tamped powder. Finally, the remaining coating material is introduced into the die and this material is then compressed to form a hard coating surrounding the core. Such a process may be carried out automatically using commercially available press-coating equipment available from manufactures such as Killian or Manesty, or the like.

Using properly calibrated equipment, it is possible to ensure that essentially all compression coated unit dosage forms formed by compression coating techniques are formed with appropriately positioned, and intact cores. However, it is possible that some cores in a batch will not be correctly positioned in dies or that during compression a core may be broken. Still further, it is also possible, particularly in

processes wherein cores are formed prior to their being coated, that core material may contaminate a die such that some of the core material finds its way into admixture with the coating material.

In any of these ways, active substance may find itself displaced from its intended position located in the core. If this occurs, the release of some of the active substance may not be correctly modulated or controlled by the coating such that the release kinetics of the active are incorrect for efficacious treatment. Also, when an active substance is an unpleasant-tasting material, any active substance finding its way on or near the surface of the medicament, or which is not sufficiently coated because of a displacement of the core, will be offensive to the patient when a tablet is placed in its mouth.

Careful calibration of press-coater machinery, and appropriate in-process control of batches of dosage forms, will tend to eliminate any imprecision in the positioning of a core in a die, and ensure that many broken cores, or core-material contaminating the coating will be avoided or at least detected. However, such calibration means generally involves an operator having to cut open a sample of the dosage forms and measure core positions, or subject the cut dosage forms to visual inspection to inspect the integrity of the core. Such in-process control is laborious, and may not pick-up the presence of small contaminant amounts of core material in the coating. Accordingly, there remains a need to develop improved aids to in-process control.

The applicant has now found that by taking the expedient of adding a colourant to the core, one can use non-invasive means, such as visible or higher energy radiation means, to locate the position and integrity of a core in a coating. Furthermore, provided a colourant is used that provides a contrast to the coating material, inspection with the naked eye will detect any core material that is contaminating the coating surface, or near surface.

The utilization of one or more colourants in medicaments is known in the art. Indeed, there are commercially available capsules, particularly for use in over-the-counter

medicaments, which consist of transparent, or substantially transparent capsules containing a plurality of coloured or differently coloured beads containing medicament. However, such colouration is used to enable a user to readily identify a particular type or brand of medicament. There is also a perception of medicinal efficacy, and of course, such dosage forms are aesthetically pleasing to the eye. Also, such medicaments employ transparent coatings, such as soft-gelatin coatings. However, the applicant is not aware of any press-coated medicament employing a coloured core. Indeed, having regard to the prior art, it is counter-intuitive to provide a compression coated tablet with a coloured core. Compression coatings are either white or coloured and are generally opaque to the naked eye.

Accordingly, the invention provides in a first aspect a medicament comprising a core containing active substance and a colourant, and a compression coating surrounding the core.

Medicaments of the present invention may be easily examined during in-process control using appropriate radiation detection means such as visible camera means or higher energy radiation such as x-ray radiation, to ensure correct placement of the core within the coating. However, in the event that some of the core material is on, or sufficiently close to, the outer surface of the medicament the contamination will be detectable to the naked eye. Both manufacturer and end user of the medicament can therefore spot defects and discard faulty medicaments. The invention therefore enables cheaper, more efficient in process control, and permits of more controlled administration of drug substances to patients.

The present invention is particularly usefully employed in medicaments that are foul tasting.

The presenting invention is also particularly useful to administer active substances in a time-controlled manner. Such dosage forms may depend for their efficacy, in terms of the control of delivery of an active substance, on the precise location of the active-containing core within the coating. A damaged core, or an imprecisely placed core,

containing active agent disposed randomly or imprecisely in the coating will release active substance in an uncontrolled manner such that a patient may not absorb the active substance in the intended manner.

Accordingly, the invention provides in another of its aspects, a method of reducing inter-subject or intra-subject variance in bioavailability of a medicament by providing to a patient in need of treatment a medicament as herein above defined.

Colourants for use in the present invention may be any of those dyes, pigments or natural colourant materials generally finding use as excipients in pharmaceutical dosage forms. Examples of suitable colorants include D&C and FD&C Blue, Red and Yellow lakes and dyes. The amount of colorant used depends upon the appearance desired and can be adjusted accordingly. Pigments including titanium dioxide, calcium carbonate, calcium sulfate, magnesium oxide, magnesium carbonate, aluminum silicate, aluminum hydroxide, talc and iron oxide may be used.

A preferred colourant for use in the present invention is red ferric oxide.

Colourants may be present in a range of from 0.1% to about 1.75%, preferably of from 0.2% to about 1.5%, and in certain preferred embodiments from 0.25% to 1.0% based on the total weight of the tablet.

The skilled person will appreciate that any active agent or combination of active agents may be employed in medicaments of the present invention, depending on the nature and severity of the condition to be treated. Preferably however, the active agent is selected from glucocorticosteroids selected from prednisone, prednisolone or methylprednisolone. These glucocorticosteroids are useful in the treatment of a variety of conditions such as rheumatoid arthritis, allergies, asthma or intestinal conditions such as Crohn's disease or ulcerative colitis.

As used above, prednisone refers to the compound and its salts or derivatives thereof, including prednisone 21 acetate.

As used above, prednisolone refers to the compound and its salts or derivatives including the 21-acetate, its 21-tert-butyl acetate, 21-succinate sodium salt, 21-stearoylglycolate, 21-m-sulphobenzoate sodium salt, and its trimethylacetate.

Methylprednisolone, as used above refers to the compound or and its salts and derivatives thereof including its 21 acetate, 21-phosphate disodium salt, 21-succinate sodium salt, and its aceponate.

The amount of glucocorticosteroid employed in tablets of the present invention will depend on the particular compound used, and the nature and severity of the condition to be treated. Typically a core may contain about 1 to 10% by weight of steroid. In the case of prednisone, it may be employed in amounts to provide a total weight per unit dosage form of 1 or 5mg, to offer convenience and flexibility of dosing.

Similarly, any conventional tabletting excipients may be employed in both core and coating. The particular core and coating excipients employed will depend on the particular release rate of active agent substance that is desired to be achieved.

Core materials may be chosen to provide an immediate release effect upon contact with moisture and as such may contain any of the known disintegrating or effervescing excipients to achieve this purpose. Alternatively, the skilled person may wish to have a slow release of active agent and therefore employ excipients, or mixtures of excipients that form a gel matrix when contacted with physiological media, thereby to permit of slow diffusion of the active substance in a sustained release manner.

In one embodiment useful in providing a rapid release of active agent from the core, the core may contain a disintegrating agent or mixtures of disintegrating agents. The disintegrating agents useful in the exercise of the present invention may be materials that effervesce in the presence of aqueous media thereby to provide the force necessary to mechanically disrupt the coating material. The disintegrants do not or

substantially do not swell or gel and prevent release of the active agent. Preferably a core contains, in addition to the active agent, cross-linked polyvinyl pyrollidone and croscarmellose sodium. Cross-linked polyvinyl pyrollidone is described above, and may be employed in the core in the amounts disclosed in relation to the core. Croscarmellose sodium is an internally cross-linked sodium carboxymethyl cellulose (also known as Ac-Di-Sol). It may be used in amounts of 5 to 30% by weight based on the core, preferably 10 to 25%, e.g. 15 to 20% by weight.

The core may additionally comprise common tablet excipients such as those described above in relation to the coating material.

Coating materials may be chosen that simply provide a water-insoluble coating that delays ingress of physiological media into the core; and the coating may contain hydrophilic or hydrophobic excipients to either increase or decrease the rate of ingress. Other coating materials may be employed that degrade upon contact with physiological environments of certain pH values, or in response to the action of physiological reactive media such as enzymes. Other coating materials may be employed that simply provided an aesthetic aspect such as pleasant tasting material excipients. Coatings may even contain colourants for aesthetic purposes or to provide a visual cue to a patient in selecting the appropriate medicament. However, the nature and amount of colourant should be selected such that there is sufficient contrast between the coating colourant and core colourant to ensure the core colourant can, be detected by the non-invasive visible, or higher energy radiation means such as x-rays.

In one embodiment, the coating is water insoluble or substantially water insoluble, and is hydrophobic. In this embodiment, the coating may contain one or more of the excipients selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, and derivatives thereof; fatty acids or their esters or salts; long chain fatty alcohols; polyoxyethylene alkyl ethers; polyoxyethylene stearates; sugar esters; lauroyl macrogol-32 glyceryl, stearoyl macrogol-32 glyceryl, and the like. The coating contains one or more hydrophobic agents. As hydrophobic agents there may be mentioned any waxy substance known

for use as a tablet excipient and having an HLB value of less than 5, and preferably about 2. Suitable hydrophobic agents include waxy substances such as carnauba wax, paraffin, microcrystalline wax, beeswax, cetyl ester wax and the like; or non-fatty hydrophobic substances such as calcium phosphate salts, e.g. dibasic calcium phosphate. Preferably the coating contains a calcium phosphate salt, glyceryl behenate, and crosslinked polyvinyl pyrollidone, or mixtures thereof.

The crosslinked polyvinyl pyrollidone is preferably present in amounts of about 1 to 25% by weight or the coating, more particularly 4 to 12%, e.g. 6 to 8%.

Glyceryl behenate, may be present as its mono-, di-, or tri-ester, and preferably the tri-ester or a mixture thereof, and is preferably present in amounts of about 5 to 85% by weight of the coating, more particularly from 10 to 70% by weight, e.g. 5 to 10%.

The calcium phosphate salt may be the dibasic calcium phosphate dihydrate, and may be present in an amount of about 10 to 90% by weight of the coating, preferably 20 to 80%, e.g. 40 to 75%.

The coating may contain other common tablet excipients such as lubricants, colourants, binders, diluents, glidants and taste-masking agents or flavourants. Examples of excipients include colourants such a ferric oxide, e.g. yellow ferric oxide; lubricants such as magnesium stearate; and glidants such as silicon dioxide, e.g. colloidal silicon dioxide. Yellow ferric oxide may be used in amounts of about 0.01 to 0.5% by weight based on the coating; magnesium stearate may be present in amounts of 1 to 20% by weight of the coating; and colloidal silica may be used in amounts of 0.1 to 20% by weight of the coating.

The invention provides in another aspect, a method of forming tablets as herein above described. The tablets may be formed on conventional press coating equipment. A series of die are arrayed on a rotating platform. The die are removably mounted in the platform such that differently sized die may be employed as appropriate. Each die is hollow to receive a lower punch. The punch is positioned within the die such that the

upper surface of the punch and the inner surface of the die define a volume for receiving a precise amount coating material. Once loaded, die is rotated on the platform until it is positioned under an upper punch. The upper punch is then urged down onto the coating material and the coating material is pre-compressed or tamped between the upper and lower punch. A pre-formed core is then fed into die to rests on the tamped coating. Conventional press coating apparatus are equipped with centering devices that enable cores to be positioned both vertically and radially. This might be achieved by a tamping process, whereby an initial amount of coating material is placed in a die and is tamped with a shaped punch that leaves an indentation in the coating material in which to receive a core. Thereafter, in a second filling operation, a precise amount of coating material is fed into the die to cover the core, and an upper punch compresses the coating material to form tablets according to the present invention.

The compression force applied during the tamping process is light and is just sufficient to provide a bed for the core and to prevent movement of the coating material as a result of centrifugal force. Subsequent compression to form the tablet may be adjusted to give tablets of requisite hardness. Preferably, this compression force is 400 kg, although this may be adjusted by +/- 30% in order to give tablets of the required hardness.

The amount of coating material fed into the die can be precisely defined having regard to the density of the coating material to ensure, after compression that the tablet is formed with the required coating thickness. Should it be necessary to change the thickness of the coating, die of appropriate internal dimensions may be placed in the rotating platform, and the amount of coating material fed into the die may be changed accordingly.

Suitable rotary tablet machines having high process speeds are known in the art and need no further discussion here.

The hardness of the tablet is preferably at least 60 Newtons, e.g. 60 to 80 Newtons, and more particularly 60 to 75 Newtons. Hardness may be measured according to a process described in The European Pharmacopoeia 4, 2.9.8 at page 201. The test employs apparatus consisting of 2 opposing jaws, one of which moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing surfaces of the jaws are flat and larger than the zone of contact with the tablet. The apparatus is calibrated using a system with a precision of one Newton. The tablet is placed between the jaws. For each measurement, the tablet is oriented in the same way with respect to the direction of the applied force. Measurements are carried out on 10 tablets. Results are expressed in terms of the mean, minimum and maximum values (in Newtons) of the force needed to crush the tablets.

Tablets having a hardness within this range are mechanically robust to withstand forces generated in the stomach, particularly in the presence of food. Furthermore, the tablets are sufficiently porous to permit ingress of aqueous media to the core.

The cores may likewise be formed using a conventional rotary tablet machine. Cores are preferably compressed under compression forces sufficient to provide cores having a hardness of about 60 Newtons or more, e.g. 50 to 70 Newtons. Cores having hardness in this range give desired release characteristics. If desired, the cores can be formed at the same time as the tablets are produced. In such case, one might employ a Manesty Dry Cota. Such a press consists of two side-by-side and inter-connected presses where the core is made on one press before being mechanically transferred to the other press for compression coating. Such equipment and techniques for making tablets using such equipment is known in the art and no more needs to be said about this here.

Cores are preferably formed according to wet granulation techniques generally known in the art. In a typical procedure, core materials are sieved and blended. Granulating fluid, typically water is then added to the blend and the mixture is homogenized to form a granulate, which is then sprayed dried or dried on a fluid bed drier to obtain a granulate with requisite residual moisture. Preferably the residual moisture content is

from about 0.4 to 2.0% by weight. The granulate is then sized by passing it through screens of desired aperture. At this stage, any adjuvants are sized and added to the granulate to form the core composition suitable for compression. The skilled person will appreciate that a coating composition can be formed in an analogous manner.

The skilled person will appreciate that granulates may be obtained having a range of particle sizes. It is preferred that the coating granulate has a fine fraction that is less than 30%. By "fine fraction" is meant granulate having particle size of up to about 63 microns.

There now follows an example that serves to illustrate the invention.

Example 1

(Preparation of a tablet)

Core:

Prednisone 8.33%
Lactose monohydrate 64.47%
Povidone 6.67%
Croscarmellose sodium 18.33%
Red ferric oxide 0.5%
Magnesium stearate 1.0%
Colloidal silicon dioxide 0.5%

Coating

Dibasic calcium phosphate dihydrate 50%
Glyceryl behenate 40%
Povidone 8.40%
Yellow ferric oxide 0.1%
Magnesium stearate 1.0%
Colloidal silicon dioxide 0.5%

The core was prepared for the press coated system as follows.

The required amounts of prednisone, and other ingredients (ex silicon dioxide and magnesium stearate) were weighed and manually sieved with a screen having 0.710 mm apertures. The components were homogeneously mixed in a Niro-Fielder PMA 25-litre mixing granulator for 6 min at impeller speed 250 rpm without chopper. A prednisone assay was performed on this premix. Subsequently, the granulating solution (purified water, 25.47 % of the weight of the dry blend was added within 4 min at impeller speed 250 rpm and chopper speed 1500 rpm, using a nozzle H1/4VV-95015 (spraying rate of 250 g/min). Mixing was continued for homogenisation and massing of the wet mass for 3 min at impeller speed 500 rpm and chopper speed 3000 rpm.

The mixed wet-granulate was then dried in a Glatt WSG5 fluidised air bed drier. The inlet temperature was maintained at 45°C during drying. The drying lasted 20 min to get a granulate with a residual moisture less than 2.5%. The yielded dry granulate was calibrated in a Frewitt MGI 205 granulator using a screen with 0.8 mm apertures for 3 min at speed 244 osc/min (graduation 7). Appropriate amounts of Aerosil® 200 and magnesium stearate were manually sieved using a screen with 1.0 mm apertures. Half of the dry granulate was put in a Niro-Fielder PMA 25-litre mixing granulator, followed by Aerosil® 200 and then by the other half of the dry granulate. The ingredients were mixed for 2 min at impeller speed 250 rpm. Finally, magnesium stearate was added and mixing was continued for 2 min at impeller speed 250 rpm.

The coating was prepared according to the process described below.

Weighed amounts of ingredients (ex magnesium stearate and silicon dioxide) were manually sieved with a screen having 0.710 mm apertures. They were placed in a Niro-Fielder PMA 65-litre mixing granulator. Then, the components were homogeneously mixed for 6 min, at impeller speed 200 rpm, without chopper. Subsequently, the granulating solution (purified water, 8.12 % of the weight of the dry blend) was added within 2 min at impeller speed 200 rpm and chopper speed 1500 rpm using a nozzle 4,9 (spraying rate of 520 g/min). Mixing was continued for

homogenisation and massing for 1 min at impeller speed 400 rpm and chopper speed 3000 rpm.

The mixed wet granulate was then dried in a Niro-Fielder TSG 2 fluidised air bed dryer. The inlet temperature was maintained at 45°C during drying. The drying lasted 33 min to have residual moisture less than 2.5%. The yielded dry granulate was calibrated in a Frewitt MGI 205 granulator using a screen having 0.8 mm apertures for 4 min at speed 244 osc/min (graduation 7). Appropriate amounts of silicon dioxide (Aerosil® 200) and magnesium stearate were manually sieved using a screen with 1.0 mm apertures. Half of the dry granulate was put in a Niro-Fielder PMA 65-litre, followed by Aerosil® 200 and then by the other half of the dry granulate. The ingredients were mixed for 2 min at impeller speed 200 rpm, without chopper. Finally, magnesium stearate was added and mixing was continued for 2 more minutes at impeller speed 200 rpm, without chopper.

The coating was press coated on active-containing core to have press coated tablets. Press coating was carried out utilising a Kilian RUD tabletting machine. First and second loading hoppers are filled up with the coating granulate. Between the two loading hoppers, the machine is equipped with a transfer system adapted to feed the cores. For each tablet, the first loading hopper supplies with about half of the quantity to be applied to the core. Then, the feeding system provides and positions a core centred in the die. Subsequently, the second loading hopper supplies with the other half of the quantity to be applied to the core. The compression step then occurs.

Equipment implemented for the manufacturing process

Equipment	Brand name/Type	Manufacturer/Supplier
Mixing granulator	Niro-Fielder PMA 25/65 litres	Aéromatic-Fielder AG, Bubendorf, Switzerland
Fluidised air bed dryer	Glatt WSG5	Maschinen und apparatebau AG, Pratteln, Switzerland

Equipment	Brand name/Type	Manufacturer/Supplier
Fluidised air bed dryer	Niro-Fielder TSG 2	Aéromatic-Fielder AG, Bubendorf, Switzerland
Granulator	Frewitt MGI 205	Frewitt SA, Granges-Pacot, Switzerland
Infrared moisture analyser	Mettler PE 360 Moisture Analyzer	Mettler Toledo AG, Greifensee, Switzerland
Multilayer tablet press	Hata HT-AP55LS-U/3L	Elisabeth-Carbide, Antwerp, Belgium
Dry coating tablet press	Kilian RUD	Kilian & Co GmbH, Cologne, Germany

Claims:

1. A medicament comprising a core containing active substance and a colourant, and a compression coating surrounding the core.

2. A medicament according to claim 1 wherein the colourant is red iron oxide.

3. A medicament according to claim 1 or claim 2 wherein the colourant is present in amounts of 0.1% to about 1.75% by weight based on the total amount of the medicament.

4. A medicament according to any of the preceding claims wherein the active substance is a glucocorticosteroid selected from prednisone, prednisolone or methylprednisolone.

5. A medicament according to any of the preceding claims in unit dosage form containing 1 or 5 mg prednisone.

6. A method of forming a tablet comprising a core containing an active substance and a colourant, and a compression coating comprising the step of compressing coating material in granulate powder form around the core.

7. A method according to claim 6 wherein the colourant is red iron oxide.

8. A method according to claim 6 or 7 wherein the colourant is present in amounts of 0.1% to about 1.75% by weight based on the total weight of the medicament.

9. A method according to any of the claims 6 to 8 wherein the active substance is glucocorticosteroid selected from prednisone, prednisolone or methylprednisolone

10. A method according to any of the claims 6 to 9 wherein the medicament is in unit dosage form containing 1 or 5 mg prednisone.

ABSTRACT

IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS

Press-coated tablets comprising a core and a coating. The core contains an active substance and a colouring agent. The invention also relates to the use of a colouring agent in such tablets to determine whether the core is centrally located within the core, to check the integrity of the core, and to ensure that there is no contaminating core material on or near the surface of the coating.